Estimating the Lost Benefits of Antiretroviral Drug Use in South Africa

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Abstract: South Africa is one of the countries most severely affected by HIV/AIDS. At the peak of the epidemic, the government, going against consensus scientific opinion, argued that HIV was not the cause of AIDS and that antiretroviral (ARV) drugs were not useful for patients and declined to accept freely donated nevirapine and grants from the Global Fund. Using modeling, we compared the number of persons who received ARVs for treatment and prevention of mother-to-child HIV transmission between 2000 and 2005 with an alternative of what was reasonably feasible in the country during that period. More than 330,000 lives or approximately 2.2 million person-years were lost because a feasible and timely ARV treatment program was not implemented in South Africa. Thirty-five thousand babies were born with HIV, resulting in 1.6 million person-years lost by not implementing a mother-to-child transmission prophylaxis program using nevirapine. The total lost benefits of ARVs are at least 3.8 million person-years for the period 2000–2005.

Key Words: antiretroviral drug use, South Africa, PMTCT, lost benefits

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South Africa is one of the countries most severely affected by the AIDS epidemic. According to Joint United Nations Programme on HIV AIDS (UNAIDS), the prevalence of HIV/AIDS in the adult population is 18.8% with approximately 5.5 million persons infected with HIV. In 2005, it is estimated that about 320,000 persons died of AIDS, almost 900 deaths per day. Approximately 1.2 million children younger than 17 years have lost 1 or both parents due to the epidemic.[1]

In 1999, President Thabo Mbeki, under pressure to provide zidovudine (ZDV or AZT) for prevention of mother-to-child HIV transmission (PMTCT) and AIDS treatment, announced that the drug was toxic and dangerous to health and that the government was not going to provide it.[2] He then questioned whether HIV was the cause of AIDS, and this broadened the debate from the usefulness of ZDV to the usefulness of all antiretroviral (ARV) drugs in fighting the AIDS epidemic because they all target HIV.[3] President Mbeki's government restricted the use of freely donated nevirapine[4] and obstructed the acquisition of Global Fund grants.[5] The facts of the case have never been denied.

Except among very few scientists, such as Peter Duesberg, the scientific community has accepted HIV as the cause of AIDS for more than 20 years.[6] HIV satisfies all 3 of Koch's postulates, the traditional standard of infectious disease causation,[7] and all of Sir Bradford Hill's epidemiological guidelines for assessing causality.[8] ZDV was tested for AIDS treatment in controlled randomized clinical trials,[9] and its side effects were clearly documented and disclosed.[10] Later studies showed that in combination with other drugs, therapy was very efficacious, resulting in the name highly active antiretroviral therapy for triple-drug cocktails.[11] ZDV was tested for PMTCT of HIV in a randomized clinical trial that showed much benefit and little risk.[12] The consensus is that ZDV's benefits very much outweigh its side effects, and its use was approved worldwide by regulatory authorities and endorsed by the World Health Organization (WHO), UNAIDS, and the US Centers for Disease Control.

We contend that the South African government acted as a major obstacle in the provision of medication to patients with AIDS. To estimate the lost benefits of ARV drug use in South Africa, we compared the actual number of persons who received ARVs for treatment or PMTCT between 2000 and 2005 with what was reasonably feasible in the country during that period. The difference, multiplied by the average efficacy of ARV treatment or PMTCT prophylaxis gives us the lost benefits of ARV use. The intention is to estimate only the lost benefits attributable to the decisions made by the leaders of the South African government. Our overriding values in choosing methods were transparency and minimization of assumptions, and we were purposely conservative.

To estimate the number of persons for whom it was reasonably feasible to use ARVs for treatment or PMTCT, we considered (1) the reduction in cost of ARV drugs over the period; (2) the increasing availability of financial resources, especially from the Global Fund and United States President's Emergency Plan for AIDS Relief (US PEPFAR); and (3) the decisions made by leaders of South African government and

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World Bank increases funding for AIDS		WHO starts prequalifying drugs	Global Fund created	US PEPFAR started	WHO '3X5' offers scale-up experts		
Glaxo offers AZT at 30% less	ARVs offered at 75-80% less Nevirapine donated free for 5 yrs	ARV patent case dropped ARVs cost $350/p/y (India)		Generic ARVs cost US$300/p/y		Single pill regimens cost US$148/p/y	
1999	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**
President Mbeki claims AZT is toxic	President Mbeki argues HIV is not the cause of AIDS			VP Zuma says ARVs deadly without nutrition			Health Minister promotes vitamins as ARV alternative
SA's government stops support to Gauteng's PMTCT pilot sites	South Africa refuses cheaper drugs offer	Nevirapine limited to 2 pilot sites / province Treatment Action Campaign sues/ wins to remove restrictions	US$72m grant to KwaZulu Natal blocked	National PMTCT program started	National ARV treatment program started	23% ART Coverage <30% PMTCT Coverage	

FIGURE 1. Time line showing events relevant for South Africa's ARV programs The top rows show that the barriers to implementing large ARV programs decreased over time, that is, ARV drug costs decreased drastically and international resources, financial and technical, increased over the period. The bottom rows show statements made by leaders of the South African government and the actual actions taken by the government. For comparison, Botswana started a PMTCT program in 1999[13] and President Mogae launched the national ARV program on December 1, 2001; by 2005, there was 85% ARV treatment coverage.[14]

their justification. This information is summarized in Figure 1. For comparison, we used, Botswana and Namibia, neighboring countries facing AIDS epidemics of similar scale and dynamics and with similar resources per capita.

To estimate the person-years lost due to lack of ARV treatment for patients with AIDS, we multiplied the following parameter estimates: First, we estimated the number of persons who were eligible to receive ARV treatment by obtaining from UNAIDS the number of deaths from AIDS in South Africa for the period 2000–2005.[15] Patients with AIDS who died without ever getting treatment lost the entire average benefit that ARV therapy provides because they can never get treated in future years. Second, the persons who actually received ARV therapy in South Africa between 2000 and 2005 are obtained from the UNAIDS and WHO "3 by 5" records (23% in 2005,[16] $<$10% in 2004,[17] 3% in 2003,[16] and less than 3% for preceding years). These estimates are consistent with estimates from the South African Department of Health, the Human Science Research Council 2005 survey, and the Actuarial Society of South Africa model.[18] Third, based on Figure 1, we considered as reasonable that South Africa could have started an ARV treatment program in 2000 treating not more than 5% of persons who needed therapy but ramping up the coverage as drugs became less expensive and more international resources became available. We use a maximum of 50% coverage of those in need by the end of 2005, an estimate that is lower than the 85% achieved by Botswana or 71% by Namibia.[19]

Last, we estimated the average life-years that ARV therapy adds to patients with AIDS in Africa. Primary studies done in Africa (including South Africa), a meta-analysis, and a comparison with the developed countries show that other than increased mortality at the start of treatment, patient responses to ARV treatment in Africa are similar to those observed in the developed world.[20] Considering outcomes of patients with low CD4 counts, the benefits of just the first-line regimen (because alternative and second-line regimens remain relatively very expensive), and treatment of opportunistic infections, we used the very conservative estimate of an average ARV treatment benefit of 6.7 years per patient. Bachmann[21] determined that ARV for disease treatment would prolong life by 6.7 years if provided late in disease development and by 9.8 years if provided earlier. This estimate is also lower than the low end of average benefits (7.8–13.3 years) that have been modeled for ARV treatment in the United States.[22]

To estimate the life-years lost by not implementing a PMTCT program in South Africa for the same period, we first estimated the number of children infected with HIV through vertical transmission. The Actuarial Society of South Africa AIDS and Demographic Model (2003) calculates a total of 68,000 infections for 2004,[23] whereas the Department of Health (South Africa) using data from Statistics South Africa estimates 105,000 infected babies.[24] To be conservative, we chose the lower estimate of 68,000 new infections per year. HIV prevalence in South Africa during 2000–2005 ranged from 18% to 21%, whereas population growth was marginal.[15] To take this into consideration, we decreased the estimate of babies infected to 60,000 per year for the entire 2000–2005 period.

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TABLE 1. Lost ARV Treatment Benefits

Year	Adult HIV Prevalence (%)	No. AIDS Deaths	Patients on ARV Treatment (%)	Patients Who Could Have Been Treated (%)	Difference (%)	Attributable Lost Lives	ARV Life-Years/Patient	Total Life-Years Lost
2000	20.1	270,000	<3	5	2	5400	6.7	36,180
2001	20.1	270,000	<3	10	7	18,900	6.7	126,630
2002	18.6	290,000	<3	20	17	49,300	6.7	330,310
2003	18.6	290,000	3	30	27	78,300	6.7	524,610
2004	18.8	320,000	<10	40	30	96,000	6.7	643,200
2005	18.8	320,000	23	50	27	86,400	6.7	578,880
						334,300		**2.2 million**

Second, based on the report by the PMTCT Task Team in South Africa (PMTCT Task Team, Concerned Child Health Workers, Johannesburg, November 15, 2005, unpublished report), the Health Systems Trust estimates that PMTCT coverage was less than 30% in 2005.[25] The government program was started in 2003, and coverage expanded in 2004 and especially in 2005, similar to the ARV treatment program. We used these guides to estimate coverage for the period, that is, less than 3% before 2003 and rising to a maximum of 30% in 2005.

Third, to estimate the percentage of women who could have been given PMTCT prophylaxis, we used data from Figure 1 and considered especially that nevirapine was offered free for 5 years in 2000; that a program giving single-dose nevirapine to mother and baby, whether given to HIV-infected pregnant women or to all pregnant women, is the most affordable of ARV programs; that a single-dose regimen is not complex to administer and can potentially be given wherever women receive antenatal care; and that 84% of women in South Africa receive antenatal care by a trained provider.[26] We assumed that it was feasible for South Africa to start a PMTCT program covering up to 5% of HIV-positive pregnant women in 2000, ramping up to about 55% coverage by 2005. This is less than the coverage achieved by both Botswana and Namibia for the period (>70%).[13]

Fourth, for estimates of efficacy of ARVs in preventing vertical transmission, we used the HIV Network for Prevention Trials 012 trial which showed that single-dose nevirapine decreased transmission by 47% compared with very short course oral ZDV in a breastfeeding population.[27] We did not consider the greater efficacy of multiple drugs or highly active antiretroviral therapy in preventing transmission.

Last, to estimate the person-years lost per case of HIV transmitted, we assumed a life expectancy of 48 years[28] and then subtracted the average survival of an HIV-infected baby without ARV treatment. A pooled analysis of babies born to HIV-infected women shows that 35% of infected babies die by the end of the first year and 52% die by the end of the second year.[29] We used 3 years as a conservative estimate of the mean survival of HIV-infected babies. We also note that the average life expectancy at birth is low partly because it already includes the high and early mortality of AIDS-infected babies. Because treatment coverage for the period was very low, we used the estimates assuming lack of treatment.

The results are shown in Tables 1 and 2. Briefly, more than 330,000 lives or approximately 2.2 million person-years were lost because a feasible ARV treatment program was not implemented in South Africa. Thirty-five thousand babies were born with HIV, resulting in 1.6 million person-years lost by not implementing a mother-to-child transmission prophylaxis program using nevirapine. The total lost benefits of ARVs are at least 3.8 million person-years for the period 2000–2005.

We tested the stability of the results if low and high estimates of the major parameters are used in the 1-way sensitivity analyses. Tables 3 and 4 show the sensitivity analyses. If we use the reasonable treatment alternative as achieving a maximum of 40% coverage instead of 50%, the number of lives lost would decrease from 334,300 to 226,800 or 1.5 million person-years. If we use a higher estimate coverage of 70% achieved by Namibia, the estimate for lost lives is 503,300 people or 3.4 million person-years. If we use the lower estimates of number of deaths per year (approximately 50,000 less than the reported estimate for each year),[1]

TABLE 2. Lost ARV PMTCT Benefits

Year	Adult HIV Prevalence	HIV Transmissions to Babies	Received PMTCT (%)	PMTCT Expected (%)	Difference (%)	Nevirapine Efficacy (%)	Excess Infections	Person-Years/Infection	Total Person-Years
2000	20.1	60,000	<3	5	2	47	564	45	25,380
2001	20.1	60,000	<3	15	12	47	3384	45	152,280
2002	18.6	60,000	<3	25	22	47	6204	45	279,180
2003	18.6	60,000	5	35	30	47	8460	45	380,700
2004	18.8	60,000	10	45	35	47	9870	45	444,150
2005	18.8	60,000	<30	55	25	47	7050	45	317,250
							35,532		**1.6 million**

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TABLE 3. One-Way Sensitivity for Lost Treatment Benefits

Variable	Attributable Lost Lives	Total Person-Years Lost (million)
Baseline calculation	334,300	2.2
Maximum treatment coverage of 40%	226,800	1.5
Maximum treatment coverage of 70%	503,300	3.4
UNAIDS lower estimates of AIDS deaths per year (less by approximately 50,000 per yr)	240,000	1.6
Upper limit of people who could have been treated including those who have not died (>1 million)	—	7.9
Lower ARV efficacy of 5.3 yrs survival on treatment	334,300	1.8
Higher ARV efficacy of 10 yrs survival on treatment	334,300	3.3

the lost lives are 240,000 or 1.6 million person-years. Instead of using the number of deaths as the only persons needing treatment, and using approximately 5 million as the number of infections in South Africa, the number of persons who could have been treated from 2000 to 2006 exceeds 1 million, translating to more than 7 million person-years lost. If we lower ARV treatment efficacy to 5.3 years of increased survival per person,[30] the person-years lost decreases to 1.8 million. If a higher efficacy of ARV treatment on survival of 10 years per person is used,[31] the person-years lost increases to 3.3 million.

Similarly, for PMTCT, if the reasonable alternative achieved only 40% coverage instead of 55% by 2005, the total number of babies infected from 2000 to 2005 is 18,000, resulting in more than 800,000 person-years lost. If we use higher coverage of 70% (still less than Botswana and Namibia), 44,000 babies are infected, resulting in 2 million person-years lost. If we consider that some babies will get infected through breastfeeding and use 18-month efficacy of nevirapine (41%),[32] 31,000 babies are infected or 1.4 million person-years lost attributable to South Africa's policies.

The main finding is that the lost benefits of not using ARVs in South Africa between 2000 and 2005 amount to at least 3.8 million person-years.

This analysis uses a direct and transparent calculation whose inputs are generally available data. For input data, we chose UNAIDS and WHO data which are generally used; data from South Africa's Health Department and the Health Systems Trust; and published data on clinical trials, meta-analyses, and observational studies. The main assumption is the number of persons for which it was feasible to provide ARVs for treatment or PMTCT from 2000 to 2005 in South Africa. We explain the basis of our estimates, consider alternatives with higher and lower coverage in the sensitivity analysis, and are purposely conservative. Although some may disagree with the exact estimates of the number of persons who could have been treated, the efficacy of ARV treatment, or the number of babies infected with HIV in a given year, the general approach is robust. Unless one argues that the Mbeki government's actions were correct, the number estimate of the person-years lost may change a little but the main conclusion of the article will hold, that is, several million person-years were lost because the leaders of the South African government chose not to implement a feasible ARV program. We chose a limited time horizon to estimate only the benefits that have already been lost and to not speculate on the future direction of AIDS treatment policy in South Africa. We also do not consider the potential lost benefits from the impact of treatment on HIV prevention via secondary transmission.

Costs are a legitimate limiting factor for any program, and there are many competing priorities for the same resources. However, the cost of ARVs decreased much starting in 1999, as shown in Figure 1. At the same time, resources dedicated for AIDS drastically increased with the creation of the Global Fund and the US PEPFAR. There is consensus that use of ARVs for PMTCT is highly cost effective in South Africa (and Africa) compared with no PMTCT prophylaxis.[33] Similarly, ARV treatment has been shown to be highly cost effective in South Africa[31] compared with no ARV treatment.[34] Using similar analyses for the treatment of patients with AIDS, others have shown that the use of ARVs is cost effective in developing countries[35,36] and also may have modest benefits in reducing incidence.[36,37] South Africa chose not to take advantage of the decreasing cost of drugs, restricted the use

TABLE 4. One-Way Sensitivity Analysis for Lost PMTCT Benefits

Variable	No. Babies Infected	Total Person-Years Lost (million)
Baseline calculation	35,532	1.6
Maximum PMTCT coverage 40%	18,000	0.8
Maximum PMTCT coverage 70%	44,000	2.0
18-month efficacy of nevirapine (41%) to include breast milk transmission of HIV	31,000	1.4
Higher ARV efficacy (75%) for multiple drugs	56,000	2.6
Higher estimate of babies infected per year (105,000) from Department of Health, South Africa	62,000	2.8

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of freely donated nevirapine, and obstructed the disbursement of US $72 million awarded to KwaZulu Natal by the Global Fund in 2002. It seems, therefore, at least from the free nevirapine and KwaZulu Natal allocation cases, that the cost of ARVs and the availability of resources were not the absolute barrier explaining why South Africa did not implement a feasible PMTCT and treatment plan. The South African government, through the Health Minister Manto Tshabalala-Msimang, has continued to the present day to divert attention from ARV drugs to nontested alternative remedies, such as lemon juice, beetroot, and garlic, sometimes even promoted as better alternatives and not supplements for AIDS treatment.

Access to appropriate public health practice is often determined by a small number of political leaders. In the case of South Africa, many lives were lost because of a failure to accept the use of available ARVs to prevent and treat HIV/AIDS in a timely manner.

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